Remarks

Paragraph [0076] of the specification has been amended to correct an error in translation.

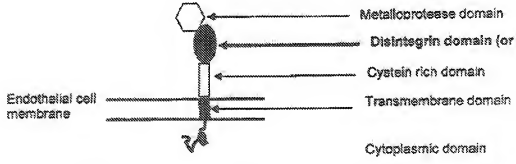
Claims 13, 17, 21 and 26 are objected to because of informalities. Specifically, the rejection states that Claims 13, 17 and 21 recite "an expression plasmid coding for a therapeutic peptide consisting of SEQ ID NO: 2," but there is no direct indication that the polynucleotide is on the plasmid. Claims 13, 17 and 21 are further objected to because the phrase "corresponding intramuscular and intratumoral site(s)" does not make it clear that the same sites that are injected are those that receive electrical impulses. Additionally, Claim 26 is objected to for reciting "a therapeutic peptide," rather than "the therapeutic peptide."

Claims 13, 17, 21 and 26 have been amended as helpfully suggested by the Examiner. Accordingly, the Applicants respectfully submit that the objections are moot.

As a preliminary matter, the Applicants provide the following regarding the subject matter of the claims and the experimental evidence demonstrating its use.

The claimed subject matter general relates to the use of a nucleic acid encoding a specific domain of Metargidin protein: the disintegrin domain, also called AMEP (page 4, paragraph [0016] and page 8, paragraph [0036]).

Metargidin belongs to the broad family of Adamalysins (page 8, paragraph [0036]), also referred to as ADAM, which are transmembrane proteins containing multiple functional domains, and notably a distintegrin domain:



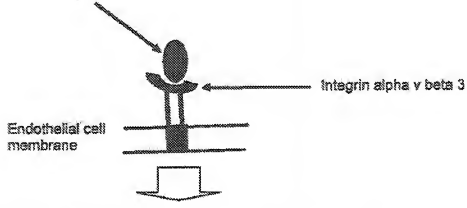
The Applicants' subject matter concerns the disintegrin domain:

The disintegrin domain of Metargidin (or AMEP) interacts with integrins, a broad family of transmembrane receptors, and especially integrin alpha v beta 3 (page 6, paragraph [0029]).

Integrin alpha v beta 3 is an adhesion molecule expressed preferentially by the endothelial cells of neovessels and certain cancerous cells. It interacts with certain compounds of the extracellular matrix, inducing the adhesion and migration of endothelial cells. The major role of integrin alpha v beta 3 in angiogenesis has been described in detail (pages 5-6, paragraph [0027]).

As illustrated below, the Applicants have surprisingly shown that AMEP, expressed as soluble recombinant protein not only blocks all angiogenic steps mediated by integrin alpha v beta 3, *i.e.*, proliferation, adhesion and migration of endothelial cells and formation of capillary structures (page 6, paragraph [0029]) but possesses also both anti-invasive and anti-metastatic capacities (page, paragraph 6 [0030]).

Disintegrin domain of metargidin (AMEP) expressed as soluble recombinant protein



- Inhibition of all steps of angiogenesis (proliferation, migration, adhesion, formation of capillary structures)
  - anti-invasive capacities
  - anti-metastatic capacities

Thus, the Applicants' claimed subject matter provides AMEP for treating cancer by inhibiting angiogenesis or invasion and/or formation of metastases (page 7, paragraphs ([0035]-[0036]) by administering a nucleic acid molecule comprising a polynucleotide sequence encoding AMEP protein (page 9, paragraph [0040]).

In this "AMEP gene-based therapy" it is not the active principle (AMEP protein) which is injected into the patient but the gene encoding for the active principle. In this therapy, the transformed cells of the patient then synthesize and secrete the active principle (AMEP protein). This "AMEP gene-based therapy" has been developed *in vivo* by the Applicants.

Indeed, the Applicants have shown that the powerful inhibitory effects of AMEP (synthesized in the form of recombinant protein) on the total set of *in vitro* experiments (the Applicants' Examples 1-5) were confirmed by the results obtained *in vivo* and performed with AMEP protein synthesized *de novo* in mammals (the Applicants Examples 6-7) (page 28, paragraph [0100]).

Claims 13, 17, 21 and 26 are rejected under 35 USC §112, first paragraph, as not being fully enabled. Specifically, the rejection states that the specification is enabling for methods of direct injection intratumorally, but is not enabled for methods of intramuscular injection.

The Applicants agree that the specification is fully enabled for methods in which plasmids containing the sequence encoding AMEP are injected into a tumor and electrotransferred at the site of injection, *i.e.*, in the tumor (*i.e.*, AMEP production site and AMEP target site are identically located). It would be understood by one skilled in the art that the AMEP protein is synthesized and secreted by transformed tumor cells and bind to alpha v beta 3 integrins which are expressed by surrounding endothelial cells of neovessels. Indeed, it is known by one skilled in the art that strong angiogenic activity takes place into/around the tumors in which intratumoral endothelial cells express alpha v beta 3 integrins (page 26 [0092]; pages 5-6 [0027]). As demonstrated by the examples in the Applicants' specification, the binding of AMEP protein to alpha v beta 3 integrins expressed on endothelial cells leads to the inhibition of blood flow around tumors cells and to their death by deprivation of oxygen and nutriments (page 10 [0044]).

The Applicants respectfully disagree with the rejection's statement that "it is not clear what relationship the intratumoral site or intramuscular site have to the intratumoral vessels." The claimed methods provide for an "AMEP gene-based therapy" in which cells transformed by plasmids containing the sequence encoding AMEP constitutes producing cells that synthesize and secrete the AMEP protein. The inventors have shown that AMEP, expressed as soluble recombinant protein not only blocks all angiogenic steps mediated by integrin alpha v beta 3, (*i.e.*, proliferation, adhesion and migration of endothelial cells and formation of capillary

structures (page 6 [0029])), but surprisingly possesses also both anti-invasive and anti-metastatic capacities (page 6 [0030]).

Thus, the claimed method provides AMEP for treating cancer by inhibiting angiogenesis or invasion and/or formation of metastases (page 7 ([0035]-[0036])) by administering a nucleic acid molecule comprising a polynucleotide sequence encoding AMEP protein (page 9 [0040]). In this "AMEP gene-based therapy," it is not the active principle (AMEP protein) which is injected into the patient, but the gene encoding for the active principle. The transformed cells of the patient then synthesize and secrete the active principle (AMEP protein) which can enter the bloodstream to have a local or systemic effect on endothelial cells of neovessels. This "AMEP gene-based therapy" has been developed *in vivo* by the Applicants. Indeed, the Applicants have shown that the powerful inhibitory effects of AMEP (synthesized in the form of recombinant protein) on the total set of *in vitro* experiments (the Applicants' Examples 1-5) were confirmed by the results obtained *in vivo* and performed with AMEP protein synthesized *de novo* in mammals (the Applicants' Examples 6-7) (page 28 [0100]).

The *in vivo* experiments described in the Applicants' Examples 6 and 7 and illustrated in Exhibits A and B, enclosed herewith, concern intramuscular injection of AMEP gene. Example 6 demonstrates plasmids containing a polynucleotide encoding the AMEP gene are first injected and electrotransferred into the tibia cranial muscle of Nude Mice (page 19 [0072]). The tibia cranial is a muscle attached to the tibia bone. The mice were then transplanted with xenografted tumor cells, namely MDA-MB-231 cells (human breast cancer cells (page 13 [0054])), by injection subcutaneously in the back (page 19 [0073]). When the tumors reached a volume of $18mm^3$, doxycycline (stable analog of tetracycline) was added to the mice's drinking water to induce expression of AMEP by cells of tibia cranial the muscle of mice.

The size of the tumors was monitored for 14 days after induction. The results show that "AMEP gene-based therapy" leads to markedly smaller tumor volumes as compared with control (78% of inhibition). This powerful inhibitory effect of AMEP on tumor growth is correlated with a significant inhibition of the number of vessels within the tumors treated with AMEP of 53.4% (page 25 [0088], Fig. 8 and Table 3).

Other *In vivo* experiments carrying out the "AMEP gene-based therapy," have been submitted during the prosecution in the frame of two declarations of Véronique Trochon-Joseph, co-inventor, made under 37 CFR §1.132 on May 1, 2009 and July 2, 2010.

Some of these experiments describes "AMEP gene-based therapy" with intramuscular injection of AMEP gene (*see* Experiments 2 and 5 of Declaration of Véronique Trochon-Joseph submitted on May 1, 2009). The powerful anti cancer effects of AMEP (inhibition of primary and metastases tumors growth) are thus fully confirmed with other tumor cells (B16F10 murine melanoma cells) and other plasmid containing AMEP gene (pORT-RDD plasmid) than those carried out in The Applicants' Examples 6 and 7 of the patent application (cf. results described above).

Some others experiences described "AMEP gene-based therapy" with intratumoral injection of AMEP gene (*see* Experiments 1, 3 and 4 of Declaration of Véronique Trochon-Joseph submitted on May 1, 2009 and experiment described in Declaration of Véronique Trochon-Joseph submitted on July 2, 2010). These experiences are explained in detail below and illustrated in Exhibit C, enclosed herewith.

Transformed tumoral cells synthesize and secrete AMEP protein. The change in tumor size is monitored.

The size of the tumors was monitored for 14 days after expression of AMEP protein. The results show that "AMEP gene-based therapy" leads to markedly smaller tumor volumes as compared with control. This powerful inhibitory effect of AMEP on tumor growth is correlated with a significant inhibition of the number of vessels within the tumors treated with AMEP.

The powerful anti cancer effects of AMEP are thus fully confirmed with other tumor cells (B16F10 - murine melanoma cells -, C9 or A375-S2 - human melanoma cells -), other plasmid containing AMEP gene (plasmids pBi, pVAX and pORT) and other site of plasmid injection (intratumorally vs. intramuscular in hind leg) than those carried out in the Applicants' Examples 6 and 7 (cf. results described above).

Hence, all these experiments demonstrate that "AMEP gene-based therapy" has a dramatic inhibitory effect on tumor growth if plasmid containing AMEP gene is injected in the tumor or in muscle (out of the tumor).

This experiment demonstrates that expression of AMEP protein by muscle cells, even if the injection site is at a distance from the tumor site, induces a dramatic inhibitory effect on tumor growth. The explanation for this experimental result is that the muscle cells into which the AMEP expressing plasmid was injected acted as "producing cells" that synthesized and secreted the AMEP protein. Hence, AMEP protein synthesized at the "AMEP production site"

has a powerful anti angiogenic effect on the "AMEP target site" even if they are differently located (hind legs vs. back).

Similarly, in Example 7, B16F10 mouse melanoma cells were injected intravenously in the retro-orbital sinus of the mice (page 21 [0076]) following the injection of AMEP containing plasmids into the tibia cranial and induction with doxycycline. Ten days later, the mice were sacrificed, the lungs were excised, and metastatic nodules were counted under a dissecting microscope. An exceptional inhibition of the number of pulmonary metastases of 74.2% after 7 days of treatment was observed in the group of mice undergoing "AMEP gene-based therapy" compared to the control group (page 25 [0091], Figs. 9 and 10).

This experiment demonstrates that expression of AMEP protein by muscle cells, even if far from the metastatic sites, induces a dramatic inhibitory effect on implantation of metastasis. This experiment is, thus, another example where the AMEP protein synthetized at the "AMEP production site" has a powerful anti metastatic effect on the "AMEP target site" (metastatic nodules), even if they are differently located (hind legs vs. lung). As well known in the art, B16F10 cells, when injected in such a way, adhere and grow in the lung and, thus, mimic a metastatic behavior. Thus, the Applicants respectfully submit that those skilled in the art would recognize this method as correlating to a metastatic tumor.

Other *in vivo* experiments carrying out the "AMEP gene-based therapy," have been submitted during the prosecution in two Declarations of Véronique Trochon-Joseph, co-inventor, made under 37 CFR §1.132 on May 1, 2009 and July 2, 2010. Some of these experiments describe "AMEP gene-based therapy" with intramuscular injection of AMEP gene (*see* Experiments 2 and 5 of the Declaration of Véronique Trochon-Joseph submitted on May 1, 2009). The powerful anti-cancer effects of AMEP (inhibition of primary and metastases tumors growth) are thus fully confirmed with different tumor cells (B16F10 murine melanoma cells) and different plasmids containing AMEP gene (pORT-RDD plasmid) than those carried out in the Applicants' Examples 6 and 7 (*cf.* results described above).

Accordingly, the Applicants respectfully maintain that the specification makes clear that the relationship that the intratumoral site or intramuscular site of injection has to the intratumoral vessels is that the transformed cells at the injection site secrete the proteins that act on the intratumoral vessels to reduce the number and formation of the vessels. While secreted AMEP proteins are expected to have little or no effect on surrounding mature endothelial cells, AMEP

proteins secreted by the transformed muscle cells will reach the systemic circulation and bind to high alpha v beta 3 integrin-expressing endothelial cells surrounding tumor site(s). The binding of AMEP protein to alpha v beta 3 integrins of endothelial cells leads to the inhibition of blood flow around tumors cells and to their death by deprivation of oxygen and nutriments (page 10 [0044]). The "AMEP gene-based therapy" intramuscularly injected and intramuscularly electrotransferred can be regarded as a systemic treatment (page 10 [0046]). The specification demonstrates that, in either intratumoral injection or intramuscular injection, the AMEP expressed by the plasmid will contact the intratumoral vessels, through direct injection or systemic circulation to inhibit the growth of intratumoral vessels.

The Applicants also disagree with the rejection's statement that "local transfer is required as concentration of DNA is low and thus is sensitive to dilution (*see* page 171, paragraph 2, of Mir, Mol. Biotechnol., 2009); and thus injection and electric pulses must be limited to the target site." The Applicants respectfully submit that the rejection's interpretation of Mir is in error. Indeed, Mir merely specifies that the whole method of gene transfer (*i.e.*, injection and electrotransfer) must be local. This is not in contradiction with the claimed methods which recite injection in the muscle and electrotransfer at the site of injection in the muscle (which is local), and injection in the tumor and electrotransfer at the site of injection in the tumor (which is also local). Mir does not teach that gene transfer must be performed in the vicinity of the target site of the protein encoded by the transgene.

Indeed, we enclose the Declaration of Lluis Mir, author of the cited article confirming these explanations and further commenting the enclosed prior article that he co-authored (André, F. and Mir, L. M. (2004), "DNA electrotransfer: Its principles and an updated review of its therapeutic applications," Gene Therapy, 11 (Suppl. 1), S33-S42) which discloses that, in a vast number of preclinical trials for various therapeutic applications, the transfected tissue was the muscle and the effect was either systemic or distant.

As supplementary evidence, the Applicants enclose the article Daud (J. Clin. Oncol., 26:5896-5903, 2008) which describes the first clinical trial in humans of gene electrotransfer therapy. In this clinical trial, a gene encoding IL-12 was electrotransferred in patients' melanoma and regression of both electrotransferred tumors and distant tumors was observed. (*See* page 5898, col. 2, paragraph 2: "There were evidence that both injected lesions *and distant noninjected lesions* regressed after the treatment regimen. [...] In 10 patients (53%) there was

evidence of a systemic response resulting in either stable disease or objective regression of untreated lesions. In addition, in three of these patients (15%), all of the distant lesions regressed completely in either the absence of any other systemic antitumor therapy (two patients) or after treatment with dacarbazine (one patient).") Accordingly, the Applicants respectfully submit that one skilled in the art would appreciate that "local transfer" does not require that injection and electric impulses be limited to the target site.

The Applicants also disagree with the rejection's statement that "gene delivery has been a persistent problem for gene therapy protocols and the route of delivery itself presents an obstacle to overcome for the application of the vector therapeutically." To support this allegation, the rejection relies on articles that are related with viral based vector therapies, which is not relevant to the claimed subject matter. The Applicants note that the rejected claims recite a plasmid, which is a non viral vector. The use of a plasmid is precisely made possible by the use of electrotransfer which is an alternative to transformation by viral vectors. *See* André, F. and Mir, L. M. (2004), "DNA electrotransfer: Its principles and an updated review of its therapeutic applications," Gene Therapy, 11 (Suppl. 1), S33-S42; *"In vivo,* DNA electrotransfer is also interesting because it allows the transfer of genes into tissues without using virus" (page S36, column 2, paragraph 1).

In any event, the Applicants note that Russell, which is quoted in the rejection at the end of paragraph 1 on page 8, describes "reasonably accurate gene delivery can be achieved by direct inoculation of plasmids..." Accordingly, the Applicants respectfully submit that one skilled in the art would not view Check, Thomas or Russell as suggesting or demonstrating that the claimed subject matter was not enabled.

Finally, the rejection states that "*in vitro* and animal models have not correlated well with *in vivo* clinical trial results in patients," and that "for humans direct administration appears necessary to reduce non-desirable side effects as well as to ensure full effect of delivered biomolecules." The Applicants respectfully submit that this analysis is erroneous and does not reflect the position of those skilled in the art, as evidenced by the Declaration of Pierre Attali submitted herewith.

In his Declaration, Pierre Attali explains that when the AMEP electrotransfer gene therapy was disclosed to the committee of experts of the French drug agency, the experts were of the opinion that the preclinical data in mice using intramuscular route suggested a systemic effect of

the AMEP plasmid. Indeed, clinical intramuscular electrotransfer of AMEP plasmid appeared to them even more preferable to intratumoral electrotransfer because long term treatment efficacy, which relies on AMEP expression, could be compromised by the death of the electrotransferred tumor cells. The Declaration of Pierre Attali demonstrates that those of ordinary skill in the art have, in fact, expected that the methods recited in the rejected claims would result in reasonably successful intramuscular and intratumoral therapies based on the preclinical data obtained in mice.

Furthermore, a Phase I clinical trial to establish safety of the treatment is undergoing and uses intratumoral administration of AMEP plasmid. The observations have already resulted in improvement of a treated melanoma lesion compared with baseline. Accordingly, this result is a further demonstration of efficacy of intratumoral administration in humans.

The Applicants submit that because preclinical data obtained in mice established efficacy of the treatment by intratumoral route, efficacy of AMEP electrotransfer gene therapy by intratumoral administration in humans is demonstrated. Intratumoral preclinical data have, thus, been confirmed in a clinical trial and preclinical data obtained in mice established efficacy of the treatment by intramuscular route, it would be reasonably expected by one skilled in the art that intramuscular preclinical data will be confirmed in clinical trial. Indeed, the experts of the French drug agency were of the opinion that AMEP electrotransfer gene therapy by intramuscular route should be favored. Accordingly, the Applicants respectfully submit that the full scope of the claims, including both intratumoral and intramuscular injection and electrotransfer, is enabled. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 13, 17, 21 and 25-30 are rejected under 35 USC §103(a) as unpatentable over Bettan, in view of Fanslow and Merkelov. The rejection states that it would have been obvious to one skilled in the art to use the disintegrin domain as taught by Fanslow, and as evidenced by Merkulov, as being SEQ ID NO: 1, in the methods taught by Bettan. In particular, on page 14 of the Official Action the rejection states that "Fanslow teaches that disintegrin domains from a variety of ADAM proteins such as metargidin can be used to inhibit angiogenesis and endothelial cell migration (*see e.g.* abstract and table 1)." The rejection concedes that Fanslow does not provide the sequence used and points to Merkulov to show that the sequence is the same as SEQ ID NO: 2.

The Applicants respectfully maintain that the claimed methods are not obvious in view of Bettan, Fanslow and Merkelov. Fanslow does not teach or suggest use of the AMEP encoding polynucleotides as recited in Claims 13, 17, 21 and 25-30. Indeed, Fanslow teaches only inhibiting integrin biological activity by contacting the integrin with an effective amount of an ADAM disintegrin domain polypeptide or inhibiting endothelial cell migration and angiogenesis by administering an effective amount of an ADAM disintegrin domain polypeptide (*see,* col. 3, lines 19-26). Administration of an ADAM disintegrin domain polypeptide is repeatedly and exclusively contemplated in Fanslow (*see,* col. 11, lines 61-64, col. 13, lines 1-5 and 16-17, 33-35, 44-47, 51-55, 56-58, 65-67, and col. 14, lines 16-18, 32-34, and *see* the titles of Examples 5 and 6 and independent Claims 1 and 28). Therefore, Fanslow does not teach or suggest using gene therapy with nucleic acids "consisting of" SEQ. ID NO: 2 and encoding disintegrin domains or that administering a nucleic acid encoding only the metargidin disintegrin domain of sequence SEQ ID NO: 2 provides a successful therapeutic modality. Accordingly, one skilled in the art would not have been motivated to administer a polypeptide consisting of the disintegrin domain of metargidin, and even less a nucleic acid encoding such a polypeptide.

Moreover, the rejection erroneously characterizes the claims of Fanslow as being "directed towards peptides consisting of just a disintegrin domain wherein the peptide is in a dependent claim linked to an Fc polypeptide." Claim 1 of Fanslow does not recite peptides "consisting of" just a disintegrin domain. Instead, Fanslow claims an ADAM-20 disintegrin domain polypeptide which comprises an amino acid sequence which may be ADAM-20 disintegrin domain (amino acids 23-305 of SEQ ID NO: 12).

Furthermore, Fanslow clearly teaches that preferred embodiments are those wherein the ADAM disintegrin polypeptide, as defined therein, is in multimeric form (col. 9, lines 8-10 and Claims 2-5). In the ADAM disintegrin domain multimers, "oligomers may be linked by disulfide bonds formed between cysteine residues on different ADAM disintegrin domain polypeptides" (*see* col. 9, lines 19-21). Fanslow teaches that an even more preferable multimer may further include ADAM disintegrin domain fused to another polypeptide, in particular, with a Fc polypeptide (col. 9, lines 34-38 and Claims 5 and 28-29) which promotes multimerization of ADAM disintegrin domain polypeptides attached thereto (col. 13, lines 28-31).

Upon reading Fanslow as a whole, one skilled in the art would have understood that Fanslow did not envision administering an ADAM disintegrin domain polypeptide consisting of

the ADAM disintegrin domain alone, but rather multimers in which ADAM disintegrin domain polypeptides are linked by disulfide bonds formed between cysteine residues of their disintegrin domains. This understanding is plainly consistent with the prevailing prejudice in the art that the disintegrin domain of adamalysin alone would not be stable upon expression due to an odd number of cysteine residues. This prejudice was already mentioned in the response filed to the Official Action of April 15, 2009, and is supported by Nath, J. Cell. Sci., 1999, 112:579-587 (previously cited).

As further evidence, the Applicants point to the Declaration of Véronique Trochon-Joseph (submitted herewith) which explains that, upon reading the document Fanslow, she would not have considered that an ADAM disintegrin domain alone could be stable on expression. Furthermore, Ms. Trochon-Joseph states that she understands the teaching of Fanslow is restricted to administering polypeptides. Gene therapy is neither disclosed, nor suggested by this document. Accordingly, the Applicants submit that Fanslow would not have suggested administering a nucleic acid encoding a polypeptide consisting of the disintegrin domain of metargidin as being a successful therapeutic modality. The subject matter claimed, therefore, represents unexpected results that were demonstrated by the Applicants' experimental data.

Merkulov fails to cure the deficiencies of Fanslow. Merkulov discloses identification of a protease with substantial similarity with ADAM proteins (col. 7, lines 10-11). This protease has the 855 amino acid long sequence shown in SEQ ID NO: 2 of Merkulov and, according to the sequence alignment in the rejection, amino acids 437-527 of this amino acid sequence are identical to the 91 amino acid long sequence SEQ ID NO: 2 according to this application. However, Merkulov does not teach that a nucleic acid encoding the protease disclosed therein, nor that a nucleic acid encoding a polypeptide consisting of amino acids 437-527 of the sequence SEQ ID NO: 2 disclosed therein, could be used in a therapeutic modality.

Indeed, Merkulov merely suggests in the paragraph spanning columns 15 and 16 that "proteases isolated from humans and their human/mammalian orthologs serve as targets for identifying agents for use in mammalian therapeutic applications, *e.g.*, a human drug, particularly in modulating a biological or pathological response in a cell or tissue that expresses the protease." Accordingly, in Merkulov, the only therapeutic modality contemplated relates to using agents that modulate the biological response in a cell or tissue that expresses the protease. Moreover, Merkulov does not teach or suggest use of a polynucleotide "consisting of" SEQ ID

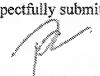
NO: 2 and its encoded protein or that this particular polypeptide would have any therapeutic activity.

The claimed subject matter would not have been obvious in view of the combination of Fanslow, Merkulov and Bettan. First, neither Fanslow nor Merkulov disclose gene therapy, and in particular, that a nucleic acid encoding a polypeptide consisting of the disintegrin domain of metargidin constitutes a therapeutic gene for the decreasing the number if the formation of new intratumoral vessels, or for treating a mammal with melanoma or pulmonary metastases.

Accordingly, one skilled in the art would not have recognized a nucleic acid encoding a polypeptide consisting of the disintegrin domain of metargidin as being a therapeutic gene to which "electrotransfer technology could be applied [...] to treat accessible tumors," as taught by Bettan. Accordingly, the Applicants submit that Claims 13, 17, 21 and 25-30 are not obvious and request reconsideration and withdrawal of the rejection.

In light of the foregoing, the Applicants respectfully submit that the entire application is now in condition for allowance, which is respectfully requested.

Respectfully submitted,



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